

Application No. 10/502,344  
Preliminary Amendment  
April 21, 2006

**Amendments to the Claims:**

The following listing of claims replaces all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (currently amended) A polypeptide comprising more than two ligand receptor binding domains of a cytokine ~~receptor~~ ligand wherein said domains are linked by a linker molecule and wherein the linker molecule comprises at least one proteolytic cleavage site.

2. (original) A polypeptide according to claim 1 wherein said cleavage site is sensitive to a serum protease.

3. (original) A polypeptide according to claim 2 wherein the serum protease is thrombin.

4. (previously presented) A polypeptide according to claim 1 wherein said cleavage site comprises the amino acid sequence LVPRGS (SEQ ID:1), or a variant thereof.

5. (previously presented) A polypeptide according to claim 1 wherein said cleavage site comprises the amino acid sequence SGGGG (SEQ ID:2), or a variant thereof.

6. (previously presented) A polypeptide according to claim 1 wherein said cleavage site comprises the amino acid sequence PGISGGGGGG (SEQ ID:3).

7. (previously presented) A polypeptide according to claim 4 wherein said cleavage site comprises the amino acid sequence: LVPRGSPGISGGGGGG (SEQ ID:4), or a variant thereof.

8. (previously presented) A polypeptide according to claim 5 wherein said cleavage site comprises a center and two copies of the amino acid sequence

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SGGGG (SEQ ID NO:2), or a variant thereof, which flank the center of said cleavage site.

9. (currently amended) A polypeptide according to claim 1 wherein said polypeptide comprises at least four ~~ligand~~ receptor binding domains of said ligand.

10. (currently amended) A polypeptide according to claim 9 wherein said polypeptide comprises 4, 6, 8, 10, or 12 ~~ligand~~ receptor binding domains.

11. (currently amended) A polypeptide according to claim 1 wherein said polypeptide comprises 3, 4, 5, 6, 7, 8, 9, or 10 ~~ligand~~ receptor binding domains of said ligand.

12. (currently amended) A polypeptide according to claim 9 wherein said polypeptide comprises greater than 10 ~~ligand~~ receptor binding domains.

13. (previously presented) A polypeptide according to claim 1 wherein said polypeptide is an antagonist to said cytokine.

14. (previously presented) A polypeptide according to claim 1 wherein said polypeptide is an agonist to said cytokine.

15. (currently amended) A polypeptide according to claim 1, wherein ~~said cytokine~~ the receptor ~~ligand~~ binding domain is the ~~ligand~~ receptor binding domain of a cytokine selected from the group consisting of: growth hormone (SEQ ID NO:18); leptin SEQ ID NO:22); erythropoietin; prolactin; interleukins (IL), IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-11, the p35 subunit of IL-12, IL-13, IL-15; granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF); ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), leukaemia inhibitory factor (LIF), oncostatin M (OSM), interferon, IFN $\alpha$  and IFN $\gamma$ .

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16. (currently amended) A polypeptide according to claim 15 wherein the binding domain is the ~~ligand~~ receptor binding domain of growth hormone and comprises SEQ ID NO:18.

17. (currently amended) A polypeptide according to claim 16 wherein the binding domain is the ~~ligand~~ receptor binding domain of leptin and comprises SEQ ID NO:22.

18. (previously presented) A polypeptide according to claim 1 wherein the linker is a polypeptide which comprises from 5 to 50 amino acid residues.

19. (original) A polypeptide according to claim 18 wherein the linker comprises from 5 to 30 amino acid residues.

20. (previously presented) A polypeptide according to claim 1 wherein the linker comprises at least one copy of the peptide GGGGS (SEQ ID NO:6).

21. (previously presented) A polypeptide according to claim 20 wherein the linker is 5 amino acids in length and consists of one copy of GGGGS (SEQ ID NO:6) (the Gly4Ser linker).

22. (previously presented) A polypeptide according to claim 20 wherein the linker is 10 amino acids in length and consists of two copies of the Gly4Ser linker (SEQ ID NO:6).

23. (previously presented) A polypeptide according to claim 20 wherein the linker is 15 amino acids in length and consists of three copies of the Gly4Ser linker (SEQ ID NO:6).

24. (previously presented) A polypeptide according to claim 20 wherein the linker is 20 amino acids in length and consists of four copies of the Gly4Ser linker (SEQ ID NO:6).

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25. (currently amended) A polypeptide according to claim 1 wherein the polypeptide is a fusion protein comprising inframe translational fusions of ligand receptor binding domains.

26. (currently amended) A polypeptide according to claim 1 comprising chemical crosslinkers wherein the chemical crosslinkers serve to link the receptor ligand binding domains.

27. (previously presented) A polypeptide according to claim 26 wherein the chemical crosslinker comprises a homo-bifunctional crosslinker selected from the group consisting of disuccinimidyl-suberimidate-dihydrochloride; dimethyl-adipimidate-dihydrochloride; and 1,5,-2,4 dinitrobenzene.

28. (previously presented) A polypeptide according to claim 26 wherein the crosslinker comprises a hetero-bifunctional crosslinker selected from the group consisting of N-hydroxysuccinimidyl 2,3-dibromopropionate; 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride; and succinimidyl 4-[n-maleimidomethyl]-cyclohexane-1-carboxylate.

29. (previously presented) A nucleic acid molecule comprising a nucleic acid sequence which encodes a polypeptide according to claim 1.

30. (previously presented) A nucleic acid molecule comprising the sequence selected from the group consisting of:

(i) the sequence represented by a growth hormone DNA (SEQ ID NO:16) tandem linked by a thrombin cleavable linker DNA (SEQ ID NO:17) or a leptin DNA (SEQ ID NO:20) tandem linked by a thrombin cleavable linker DNA (SEQ ID NO:17);

(ii) a sequence which hybridises to the sequence of (i) above and which has cytokine receptor modulating activity; and

(iii) a sequence which is degenerate as a result of the genetic code to the sequences defined in (i) and (ii) above.

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31. (previously presented) A nucleic acid molecule which hybridises under stringent hybridisation conditions to the sequence represented by a growth hormone DNA (SEQ ID NO:16) tandem linked by a thrombin cleavable linker DNA (SEQ ID NO:17) or a leptin DNA (SEQ ID NO:20) tandem linked by a thrombin cleavable linker DNA (SEQ ID NO:17).

32. (previously presented) A polypeptide encoded by the nucleic acid molecule according to claim 29.

33. (original) A polypeptide according to claim 32 wherein said polypeptide is modified by deletion, addition, and/or substitution of at least one amino acid residue and said modification enhances the antagonistic or agonistic effects of said polypeptide with respect to the inhibition or activation of receptor mediated cell signalling.

34. (previously presented) A vector comprising the nucleic acid molecule of claim 29.

35. (original) A vector according to claim 34 wherein said vector is an expression vector adapted for prokaryotic or eukaryotic gene expression.

36. (previously presented) A vector according to claim 34 wherein said vector further encodes a secretion signal linked to the polypeptide to facilitate purification of the polypeptide.

37. (previously presented) A method to prepare a polypeptide according to claim 1, the method comprising:

- (i) growing a cell transformed or transfected with a nucleic acid of claim 29 in conditions conducive to the manufacture of said polypeptide; and
- (ii) purifying said polypeptide from said cell, or its growth environment.

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38. (previously presented) A cell transformed/transfected with a vector comprising the nucleic acid of claim 29.

39-42. (canceled)

43. (previously presented) A pharmaceutical composition comprising the polypeptide according to claim 1, and a pharmaceutically acceptable carrier, excipient, or a diluent.

44. (previously presented) A pharmaceutical composition comprising the nucleic acid molecule of claim 29 and a pharmaceutically acceptable excipient.

45. (previously presented) A method for treating a disease selected from the group consisting of: acromegaly; gigantism; GH deficiency; Turners syndrome; renal failure; osteoporosis; diabetes mellitus; cancer; obesity; insulin resistance; hyperlipidaemia; hypertension; anaemia; an autoimmune disease; an infectious disease; an inflammatory disorder, and rheumatoid arthritis, wherein said method comprising administering to a patient in need thereof a pharmaceutical composition according to claim 43.

46. (previously presented) A method for treating a disease selected from the group consisting of: acromegaly; gigantism; GH deficiency; Turners syndrome; renal failure; osteoporosis; diabetes mellitus; cancer; obesity; insulin resistance; hyperlipidaemia; hypertension; anaemia; an autoimmune disease; an infectious disease; an inflammatory disorder, and rheumatoid arthritis, wherein said method comprising administering to a patient in need thereof a pharmaceutical composition according to claim 44.